WAR GASES, AND OTHER NOXIOUS GASES, AND FUMES:

A variety of noxious fumes and gases have been suggested by ~~various workers~~ as being of etiological significance in the development of cancer of the lower respiratory tract. Kikuth (1925) and Hünermann (1929) reported a few cases of respiratory cancer ~~developing~~ in industrial workers exposed to fumes from mineral acids and alkalis. Betke (1933) reported 3 cases of pulmonary cancer in industrial workers who had been exposed to fumes of sulfuric and hydrochloric acids for periods of 28, 31, and 42 years respectively. In contrast to these findings, Koelsch (1934, 1937, 1938) studied 100 workers exposed to strong mineral acids during their manufacture and found no cases of lung cancer; in a parallel study, no cases of lung cancer were found among workers in acid-consuming industries. Winternitz, Smith, and McNamara (1920a) were unable to produce lung tumors in rabbits by insufflation of hydrochloric acid.

A carcinogenic action for chemical warfare agents has been alleged by some workers. Kikuth (1925) considered that poisoning by chlorine, phosgene, diphosgene, mustard gas and thioglycol chloride are of etiological significance in the development of cancers. Brockbank (1932), Klotz (1938), and Derichanoff (1932) considered the same possibility. Katz (1938) reported that of 138 cases of primary cancer of the lung in veterans of World War I, 10 had suffered exposure to chemical warfare gases. Brockbank (1932) observed that of 64 cases of primary bronchiogenic carcinoma, 4 had been gassed seriously during that war. On the other hand, in many extended studies of primary

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lung cancer, no association of war gassing with the incidence of lung cancer has been detected (see, for example, Berblinger, 1925, 1931; Probst, 1927). According to Hueper (1942), Nolan (1932) was unable to establish any interrelation between a history of war gassing and the development of primary lung cancer from a statistical investigation of the records of the U. S. Army and of autopsy reports of ~~Army~~ veterans ~~in the United States~~.

Koontz in work cited by Koelsch (1935) found that several hundred dogs exposed to various chemical warfare agents in almost lethal concentrations for periods up to several years, had no permanent injury to the lower respiratory tract. On the other hand, Richter and Adelheim ~~Adelagim~~, according to Hueper (1942), found epithelial metaplasia of the bronchial mucosa in animals exposed to chlorine gas and phosgene.

War gas poisoning produces in humans chronic, ~~pathologic~~, pulmonary lesions, including obliterative bronchiolitis and epithelial bronchiolar metaplasia, and some investigators look upon these symptoms as being possibly precancerous in nature (see Hueper, 1942). Hueper (1942) has concluded that exposure to chemical warfare agents and to the other noxious gases and fumes mentioned above, may have some slight etiological significance in the development of pulmonary tumors in isolated cases. On the other hand, no evidence is at hand that these factors are of any significance in the general increase in the incidence of lung cancer in the last two decades.

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TUBERCULOSIS; [illegible]

Tuberculosis of the lung has been suggested by ~~a number of~~ some. workers as being ~~one of the~~ a causative factor in bronchiogenic carcinoma. Ewing (see 1940), for example, on the basis of the occasional co-existence of the two conditions, concluded that tuberculosis was one of the important etiologic factors in lung cancer. ~~bronchiogenic carcinoma.~~

In a series of 139 cases of lung cancer, Simpson (1929) reported the co-existence of tuberculosis in 47 cases, but the tubercular process was active in only 6 of these cases. Derischanoff (1932) found tuberculosis to co-exist with lung cancer in 16.7 percent of his autopsy series. Kraft (1934) found these two conditions present together in 46.7 percent of his 150 cases of primary lung cancer. Frissell and Knox (1937) reported the presence of tuberculous lesions in 18.6 percent of their cases of bronchiogenic carcinoma.

In contrast to the studies reported above, many other workers have recorded a much lower degree of association of tuberculosis with carcinoma of the lung. Seyfarth (1924) found lung cancer ~~of the lung~~ associated with pulmonary tuberculosis in only 2 percent of his cases. Breckwoldt (1926) found such association in 8.5 percent; Wahl (1927), in 9.8 percent; Probst (1927), 5 percent; Olson (1935), active tuberculosis in 1.6 percent, healed tuberculosis in 5.9 percent, or a total of 7.4 percent; ~~and~~ Matz (1938), 2.1 percent; ~~and~~ Schairer and Schöninger (1943) in 5.4 percent; and Attinger (1950) in 1.6 percent.

A causative relationship between tuberculosis of the lung and cancer of the lung was doubted by Simons (1933, 1937), Ferenczy and Matolay (1927), Klotz (1938), Hueper (1942), and by Fried (1935, 1948). Olson (1935) observed that the incidence of tuberculosis in

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cancer of the lung corresponds roughly to the known incidence of tuberculosis in unselected cases, and Fried (1932) reported a lower incidence of malignancy in a series of tuberculosis cases than in a group of non-tuberculous patients.

Hueper (1942) concluded although that occasionally a bronchiogenic carcinoma originates from the metaplastic epithelium of a tuberculous bronchiectasis, usually tuberculous infections of the lung have no causative relation to the majority of pulmonary malignancies, and do not play any role in the production of the observed increase in lung cancer. He further observed that such an interrelation is made less plausible because the mortality from tuberculosis has been reduced and the incidence of severe tuberculous lesions of the lung has been diminished.

Klotz (1938) concluded, "While tuberculosis cannot be considered a common etiologic factor, it would seem reasonable to agree that those carcinomata reported as arising in tuberculous cavities are probably the result of the chronic inflammatory changes and consequent metaplasia, but this does not imply any carcinogenic effect on the part of the tubercular bacillus itself".

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INFLUENZA & OTHER INFLAMMATORY DISEASES:

In the decade 1920-1930, ~~a number of~~ Some workers suggested a causal relationship between certain bacterial infections and carcinoma of the lung. The possible influence of influenza, which was epidemic during the period 1918-1920 in many parts of the world, was reported by some workers (Askanazy, 1919; Winternitz, 1920a, 1920b; Mois, 1929; Barron, 1922; Probst, 1927; Berblinger, 1925, 1931). Klotz (1938) pointed out that peculiar lesions suggesting precancerous changes had long been recognized as occurring in the lungs in association with inflammatory conditions. Winternitz (1920) described such changes following influenza as taking the form of active epithelial proliferations which often advance to an extent resembling "infiltrating, malignant epithelial neoplasm". Winternitz (1920b) observed similar changes in the lungs of rabbits following insufflation of hydrochloric acid. Askanazy (1919) observed squamous metaplasia of the bronchi in individuals dying from influenza, and thought this metaplasia was pre-cancerous as did Teutschländer (1923) and Klotz (1927).

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Hueper (1926, 1929) observed that no increase in lung cancer was noted after the great influenza epidemic of 1888-1889, and that the most rapid increase has occurred years after the epidemic of 1918-1919.

Dungal (1950) reported that in Iceland lung cancer is still a rare disease, the incidence being the same order as that seen in many European countries at the beginning of the century. On the other hand, the incidence of bronchitis and influenza is more frequent in Iceland than in most civilized countries. He concluded therefore that there is no causal relation between the common respiratory infections and lung carcinoma. Kerlig (cited by Matz, 1938) had earlier employed similar reasoning.

Also, most clinical studies have failed to demonstrate any condensing relationship between influenza and bronchial tumors (Seyfarth, 1924; Staehelin, 1925; Kikuth, 1925; Breckwoldt, 1926; Hanf, 1927; Klotz, 1936, 1938; Schairer and Schöniger, 1943; Fried, ~~1936~~ 1935, 1948). Hueper (1926) and Weller (1929) commented that

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a peak in the incidence of cancer of the lung was reached in some areas of the world by 1918, and that no significant increase in the incidence of this cancer was observed following the influenza epidemic of that year. Fried (1932, 1948) as well as many other workers have repeatedly observed that few patients with carcinoma of the lung give a history of influenza and doubt can be expressed as to the probability of a single acute infection such as influenza initiating changes leading to the development of malignancies.

Müller (1940) pointed out that the incidence of lung cancer in Cologne, Germany in the year immediately following an epidemic of grippe in 1927 showed a marked increase. Earlier, Berblinger (1925) considered that the increase in lung cancer observed in Jena and in other cities in Germany following the first World War might be etiologically connected to a great epidemic of grippe in the same war. Müller in a series of 47 cases of primary cancer of the lung concluded that any connection between the history of grippe and the development of primary carcinoma of the lung was not clear and could only be elucidated through extensive, controlled studies.

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Steiner and Loosli (1950) studied the ~~carcinogenicity~~ effect of human influenza virus ([redacted] APR-8 strain) inhaled as a mist on the production of lung tumors in inbred mice. The resulting infection ~~resulting~~ produced [redacted] tumor-like epithelial hyperplasia during the recovery stage, and some lung lesions induced by the influenza persisted throughout the life of the animal. However, these changes did not ~~eventually~~ eventuate in lung tumors in mice of low ~~incidence~~ susceptible strain (C57 Black), and neither was the infection carcinogenic nor the epithelial hyperplasia pre-cancerous in the high spontaneous strain A animals. In fact, in some experiments there was the suggestion that the influenza infection might be anti-carcinogenic (lowered percentage of tumors and/or lengthening of tumor induction time in experimental animals).

SYPHILIS OF LUNG:

Simpson (1929) and Jaffe (1935) have recorded ~~some~~ an occasional association of syphilis of the lung with bronchial cancer, but such association is rare, and according to Klotz (1938) probably bears no causal relationship other than that of a chronic irritant.

PARASITIC INFESTATIONS:

Fried (1932) has pointed out that ~~the~~ association of pulmonary cancer ~~and~~ with parasites is extremely rare, even though ~~parasitic infestations~~ parasites have been reported to initiate neoplastic lesions at other sites. Eggers (1931) cited one case of [redacted] carcinoma associated with trichinosis.

[redacted] such infestation has

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SILICOSIS

~~Silicosis and Related Conditions~~:

Caps

Inhalation of silica dust has been mentioned often as a possible etiologic agent in bronchiogenic carcinoma, and cases of silicosis co-existing with cancer of the lung ~~as reported~~ are scattered in the literature (Davidson, 1930; Olson, 1935; Schmorl, 1923a, 1923b, 1928; Seyfarth, 1924; Egbert and Geiger, 1936; and papers cited by Klotz, 1938; and by Hueper, 1942, 1950a). However, many other ~~studies~~ investigators have concluded that this association is merely coincidental.

Simpson (1929) and Passey and Holmes (1935) observed that primary cancer of the lung is relatively rare among the gold miners of South Africa, while silicosis is very common. Vorwald and Karr (1937, 1938) confirmed these observations and reported a lower incidence of lung cancer among silicotics than in the general population. Schulte (1930) and Schulz (1935) studied the incidence of lung cancer among miners in the Ruhr District where silicosis has a very high incidence and concluded that silica dust is not a factor in the genesis of primary lung cancer. Schulte (1930) in fact concluded that the lungs of silicotics are less susceptible than normal lungs to the cancer process.

Schairer and Schöniger (1943) on the basis of statistical study of the lung cancer cases autopsied at Jena, concluded that the incidence of cancer is no higher ~~than~~ in persons exposed to silicosis than in the general population in the same region in Germany. E. L. & M. N. Kennaway (1947) reported in an extensive study of the incidence [illegible] lish death

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certificates for the period 1921-1938 that the occupations in which there was a liability to silicosis did not show an incidence of lung cancer higher than that for all workers. Rüttner (1949) recently concluded from a controlled statistical study that bronchial carcinoma does not occur more frequently in silicotics than in the average population.

It must be concluded that the burden of existing evidence does not support the view that inhalation of dust containing silica can be considered an etiologic factor in the genesis of human pulmonary carcinoma; however, the relevant animal studies should be discussed in this connection.

Willis (1928) and Willis and Prutsart (1928) observed at autopsy adenomatoid formation surrounding the bronchi in several animals of a series of guinea pigs exposed to silica dust for 50 hours per month for a period of 18 to 31 months, but did not observe any true pulmonary cancers. They held that the observed lesions might be a hyperplastic response to the irritating silica, but, as Hueper (1942) pointed out, such lesions occur spontaneously. Negative results were also obtained by Vorwald and Karr (1937, 1938) in 3,338 animals of various species (guinea pig, rabbit, rat, mouse, cat, and chicken) exposed to various dust (most of them containing silica) for periods up to 749 days. Campbell (1940, 1941, 1942a, 1942b) observed some increase in pulmonary tumors in mice by chronic inhalation of siliciferous dust and this incident did not seem to become greater

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observed.
that the negative results with silica obtained by other workers may be attributed to the fact that the animals were not allowed to live to the tumor-producing age and to the natural insensitivity of some animal strains and species that were employed.

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ASBESTOSIS:

Asbestotic pneumoconiosis resulting from prolonged occupational inhalation of asbestos dust or fibres has been recognized as an industrial hazard in recent years as the use of asbestos has increased. In recent years, consideration has also been given to a possible carcinogenic action of asbestos upon the lungs. Kennaway and Kennaway (1936) did not find any cases of lung cancer in asbestos workers in an analysis of 18,280 death certificates for cancer of the lung and larynx in males from England and Wales for the period 1921-1932, but in a later paper (1947) extending the study through 1938, chronic exposure to asbestos dust seems associated with the incidence of lung cancer. Since 1933, cases have been reported of carcinoma of the lung associated with a history of asbestosis or at least of chronic exposure to asbestos by Gloyne (1933, 1935, 1936), Wood and Gloyne (1934), Lynch and Smith (1935, 1939), Lynch (1937), by Egbert and Geiger (1936), by Horning (1938), by Nordmann (1938, 1939), by Linzbach and Wedler (1941), by Holleb and Angrist (1942) and by Homburger (1943). Many workers feel that the incidence of lung cancer among asbestotics at autopsy is relatively high; ranging from 17 percent (Nordmann, 1938) to 20 percent (Wood and Gloyne, 1934). Wedler (1939, 1943) found 14 lung cancer cases (4 in females) in 92 autopsies of asbestosis workers, and reported as had Lynch and Smith (1935, 1939) that an appreciable portion of the cases in which asbestosis and lung cancer co-exist are in relatively young men. The latter workers had suggested that a relationship may exist between the time and length of exposure to asbestos dust and

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the appearance of pulmonary neoplasms. Hueper (1942, 1950) concluded that the available evidence is suggestive of an association of lung cancer with occupational exposure to asbestos. He observed that nothing is known about the actual causative mechanism through which asbestosis may produce such epithelial lesions, and may transform them subsequently into malignant growths.

Nordmann and Sorge (1941) exposed 100 white mice to asbestos dust for a total of 67 to 80 hours over a period of six weeks or for a total of 72 hours over a 13-week period. At the end of 20 weeks, 61 animals survived for examination. Of these, 20 percent showed a keratinized multi-centric squamous epithelial lung carcinoma and 42 to 57 percent showed epithelial lung neoplasms in all stages. These findings, the authors concluded, supported the view held by Nordmann (1938) and by other workers that chronic exposure to asbestos dust may be a factor in the causation of lung cancer in asbestos workers.

After reviewing the literature on asbestosis, Hueper (1942) stated:

> "An evaluation of the evidence presented reveals certain features connected with these cases which are suggestive of an occupational causation. There is an incidence of lung cancer in asbestosis of the lung which is definitely excessive. The relatively small number of necropsies on which this conclusion is based represents an urgent indication for more extensive post-mortem examinations in cases of asbestosis; especially considering that pulmonary malignancies seen in previously reported cases were, in several instances, very small and were coincidental observations... Nothing is known about the actual causative mechanism through which asbestosis may produce such epithelial lesions, and may transform them subsequently into malignant growths."

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SIDEROSIS

~~Siderosis of~~ Occupational pulmonary ~~lung~~ siderosis is caused by the deposition of iron or iron oxide in the lung, and a relationship between ~~pulmonary siderosis~~ this condition and primary lung cancer has been suggested by several workers. According to Kennaway and Kennaway (1936), workers exposed to metal dust (metal grinders) have in England and Wales an incidence of lung neoplasms 2.25 times that of ~~the~~ the general population. A similar relationship was suggested by Turner and Grace (1938), Campbell (1934, 1936, 1937, 1940), Vorwald and Karr (1937, 1938), and Simons (1937).

The relatively small number of human lung carcinomas reported ~~to~~ follow ing occupational inhalation of iron dust or iron-containing minerals is too small to permit any definite conclusion, ~~but~~ but existing evidence suggests the need ~~of~~ for further study to establish whether or not the relationship is causal or merely coincidental. That the association of the inhalation of iron dust or iron-containing mineral dust may be causal is suggested by the finding of Campbell (1936, 1937, 1940) that mice ~~xxxxxxxxxxxxxxxx~~ dusted with iron oxide or with siliceous material showed an increase ~~in the~~ incidence of lung neoplasms, and this incidence seemed not to be further increased by co-administration of methylcholanthrene.

On the other hand, Vorwald and co-workers (1950) exposed normal and tuberculous guinea pigs, and normal rats and rabbits to iron oxide accompanied by four percent silica for periods up to three years and observed no pulmonary tumors.

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BERYLLIUM DUSTS:

Gardner (1946) and Lansa (1945) have reported sarcomatoid granulomas in lungs of workers exposed to the dust of beryllium compounds in the manufacture of lamps and other electronic products. Gardner has concluded that the actual causation of the pulmonary reactions ~~in human lung~~ associated with beryllium and its compounds is unknown, but some animal evidence suggests that other factors are also at work. No proliferative responses were observed in dogs, rabbits, guinea pigs, white rats, and white mice when zinc beryl silicate, beryllium oxide, and mixed phosphors (Sr, Ba, Cd) ~~was~~ were inhaled or injected, but rabbits injected intravenously with zinc beryllium silicate and insoluble beryllium oxide almost invariably developed malignant sarcomas of the bone within five to seven months. Davies and Harding (1950) have reported a similar findings in general. According to unpublished work of Hueper, cited by Spencer (1950), the recent death rate due to lung cancer among workers exposed to beryllium dust in the manufacturing industries is very high, and further studies are in progress at the National Cancer Institute to determine to what extent, if any, beryllium dusts have carcinogenic properties.

and Barnes (1948) observed bone sarcomas in rabbits ~~exposed~~ injected intravenously with zinc beryllium silicate, beryllium silicate, and with ~~powdered~~ divided beryllium metal,

finally

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ARSENIC:

As observed elsewhere in this review in the development of lung cancers in miners employed at Schneeberg and Joachimsthal in which the ores are not only radioactive (uranium) but contain arsenic and cobalt as well, arsenic has been implicated by some workers as being responsible in part for the high incidence of lung cancer observed. Saupe (1930, 1933) has studied at length the incidence of pulmonary cancer in arsenic workers in smelters and processing plants at Freiberg in Saxony. Of 40 workers examined by Saupe, 12 workers showed mild pneumoconiotic changes. Two of these workers died with carcinoma of the lung associated with pneumoconiosis. Saupe did not believe that his limited evidence permitted a decision as to whether occupational exposure to arsenic or its oxides was of etiologic significance in the genesis of primary cancer of the lung.

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Kennaway and Kennaway (1947), on examination of English death certificates, concluded that occupational exposure to arsenic dust or fumes might be associated with an increased incidence in lung cancer. Association of arsenic poisoning by occupational or medicinal exposure and the occurrence of lung cancer has been reported by Hunter (1939, 1946a, 1946b), by Merewether (1944), by Henry (1946), by Montgomery and Waisman (1941), by Von Pein (1938; 1943), ~~and~~ by Goeckemann and Wilhelm (1940) and by Semon (1945). But other workers have pointed out the lack of correlation of lung cancer and arsenical exposure in orchardist (Neal and co-workers; Dressen and co-workers, 1938; Edwards, 1941; 1941), and among arsenic-eating mountaineers of Tyrol and Syria (Oppenheim, 1943).

The experimental evidence in animals regarding a possible carcinogenic effect for arsenic is inconclusive. Cholewa (1935) reported the development of lung tumors in two of twenty white mice fed a diet containing arsenic oxide for a period of one year.. This experimental result, as Hueper (1942) has observed, is of little significance as an incidence of more than 10 percent lung tumors is not unusual in normal mice more than one year old. Inconclusive or negative results were obtained in other animal experiments by Leitch and Kennaway (cited by Hueper, 1950a), by Roffo (1946) and by Hueper (1943b, 1946b). Hueper (1950a) remarked that the short life span of experimental animals, however, prevents the arsenicals from taking proper effect or excretion of arsenic in the hair of furry animals gives unsatisfactory results.

It must be concluded that the available evidence is inconclusive as to whether or not arsenic or its compounds are of etiologic significance in the genesis of primary cancer of the lung.

Certain considerations of the arsenic content of tobacco [illegible]

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CHROMATES:

Although lung cancer was found in men with an history of exposure to chromium compounds occasionally, as late as 1932 Lehmann maintained that the association was merely coincidental. Pfeil (1935), Alwens, Bauke and Jonas (1936), Teleky (1936, 1937a, 1937b, 1938), Gross (1936), Bauke (1936) and Koelsch (1937, 1938) among later workers found such an appreciable number of lung cancers among workers in chromate plants in Europe as to suggest a possible causal relationship.

Machle and Gregorius (1948) found that 21.8 percent of all deaths in the chromate industry in the United States were due to cancer of the respiratory system. This percentage is 16 times the expected 1.3 percent. The individual ratios in 5 out of 6 plants range from 13 to 31 times the normal. In 5 of these 6 plants, the death rate from lung cancer in the age group 50 years and under ranged from 20 to 27 times that for a comparable industrial group, while for the age group over 50 years it ranged from 10 to 40 times. Of 193 deaths studied, 66 were due to cancer (34.2 percent), and of these 42 were due to lung cancer. In this series, the average number of years of exposure to chromates before development of cancer of the respiratory system was 14.5 years. This agrees well with the value of 15 years cited by earlier European investigators. One of the six plants studied handled principally basic chromates, chromic acid and tanning compounds, and no monochromate salts, as did the other five plants. In this single plant, no deaths were recorded due to lung cancer, and Machle and Gregorius suggested that only a certain form of chromates, namely the monochromates, may have carcinogenic activity.

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Hueper (1950b) from the official statistics available for Germany up to 1939 reported a total of 39 cases of lung cancer among about 1,000 chromate workers employed in several plants for a sufficiently long time to be affected. He concluded that the incidence of lung cancer among these chromate workers, living and dead, was about 4 percent, according to the uncorrected figures, and was in all probability actually higher. This rate, according to Hueper, was at least four times that for the general adult population.

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Teutschlaender (1937), Gross (1936), and Lukanin (1930), were unable to produce tumors in animals exposed to inhalation of chromate dust. The only experimental evidence for a possible carcinogenicity of chromium or its compounds is the work of Schinz (1942) in which metallic chromium was implanted into rabbits' thighs, and four years later sarcomas at the site of implantation and carcinomas of the lung were observed in a few animals.

Although the number of cases of lung cancer in which a history of inhalation of dust containing chromium or its compounds (chromates especially) is small, some of the studies are well enough controlled to suggest that inhalation of chromium and its compounds may be an occupational hazard worthy of the closest study. Further inconclusive evidence concerning a possible carcinogenic action for chromium or its compounds has been discussed by Hueper (1942, 1950).

NICKEL CARBONYL:

Certain operations in the production of nickel metal large scale production lead to the formation of volatile nickel carbonyl. A few workers have reported a high incidence of carcinoma of the lungs and of other portions of the respiratory system in workers exposed to vapors containing nickel carbonyl. The brief literature bearing on a possible causal relationship between the inhalation of nickel carbonyl and the genesis of lung cancer has been reviewed by Hueper (1942, 1950b) and is not further discussed in the present survey. The need for further and more extensive control studies are needed before any decision can be made as to whether or not nickel carbonyl possesses any carcinogenic action in the human

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Hueper (1951) in recent work injected powdered nickel into bone cavities or into the lung cavities of rats. Cancerous reactions developed in thirty percent of rats surviving more than eight weeks. In several of the animals bone cancers as large as golf and tennis balls developed.

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MISCELLANEOUS OR

OCCUPATIONAL EXPOSURE TO DUST OF UNSPECIFIED NATURE:

A.

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Brockbank (1932) reviewed the occupational incidence of primary lung cancer in 698 cases reported in the literature in which the diagnosis was verified post-mortem. He observed that in many recorded cases the occupation history was inadequate because only the immediate occupations prior to death were recorded and these may have no connection with the etiology of cancer, while in contrast some earlier occupations may be highly significant. Brockbank concluded that lung cancer predominated in the laboring classes, although no single occupation could be implicated. In a closely studied series of 62 cases, nine (14.5 percent) had dusty jobs; eighteen (29 percent) worked among gases and fumes; and four were gassed in World War I.

Rosedale and McKay (1936) found 75.4 percent of 57 cases of lung cancers had been employed in occupations requiring exposure to dust or other irritating atmospheric factors. Frissel and Knox (1937) report that in their series of 46 cases of primary lung cancer, only three had been exposed to dusty atmospheres.

Schairer and Schöniger (1943) studied the occupational history of lung cancer cases seen at the Jena Pathological Institute. These workers concluded that there was no marked departure of the occupational distribution in lung cancer cases in this series from that of the general population in the same region of Germany. Of 75 cases studied by these workers, 13 were exposed to stone dust and 10 to metal dust, while 52 were engaged in dust-free occupations.

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all cases

Mechanical Trauma:

A history of direct trauma resulting in [redacted] injury to pulmonary tissue associated with lung neoplasms has been reported [redacted]ly by a number of workers including Kikuth (1925), Adler (1912), Weller (1929), Wells and Cannon (1930), Gillespie (1932), Graham and Singer (1933), Fischer-Wasels (1933, 1936), Gomez (1937), Pilgerstofer (1937), Fischer and Fenster (1938), and Klotz (1938).

Simons (1937) in a review of literature collected only a total of 19 cases of carcinoma of the lung associated with a history of mechanical trauma.

Jaffe (1935) recorded that in a closely studied series of ~~at about~~ 100 cases of lung cancer, none showed a [redacted]te relation to a preceding trauma. In one case, a bullet was encapsulated in the right lower lobe for several years, and a squamous cell carcinoma developed in the left lung. He concluded that these findings excluded the possibility that an old injury might be related to a lung tumor.

The small number of lung cancer cases in which a traumatic origin has been alleged makes it clear that mechanical trauma of the chest can be of little importance in the special etiology of lung cancer. As Hueper (1942) and Klotz (1938) implied, the co-existence of a history of trauma and of lung cancer is probably merely coincidental in most cases - especially in view of the low frequency in which such association can be demonstrated clinically or pathologically. The question of lung cancer and mechanical trauma has been discussed at greater length by Hueper (1942).

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OTHER CONSIDERATIONS of Occupational & Environmental Factors

Bonser (1929), Hruby and Sweany (1933), and Passey and Holmes (1935) concluded that their efforts to establish an occupational correlation for the incidence of primary cancer of the lung were, on the whole, disappointing.

Brockbank (1932) concluded that cancer of the lung is primarily a disease of the laboring classes. Klotz (1938) accepted Brockbank's observation with reserve, since the majority of patients admitted to most large hospitals and institutions are of the laboring class, while the well-to-do patronize private hospitals and usually fail to come to autopsy.

Simons (1937) stated that until more information on the relation of occupation to the genesis of lung cancer is available, industrial hazards cannot be accorded etiological significance - except that they may involve chronic irritation of the lungs.

Matz (1938) in a study of 138 lung cancer cases seen by the Veterans Administration of the U. S. Government found that 50 (36 percent) gave a history of being connected with occupations or industries in which there was a possibility of irritation and traumatization of the respiratory tract. Matz concluded, "The fact that so large a percentage had been engaged in occupations which caused them to be exposed to chronic irritation of the respiratory tract is suggestive that such occupations may have a causative part in the [redacted]

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Schairer and Schöniger (1943) investigated the occupational hazards of 72 lung cancer cases seen at the Jena Pathological Institute. These workers concluded that there was no marked departure of the occupational distribution in lung cancer cases from that of the general population in the same region.

E. L. and N. M. Kennaway (1947) reported a study ~~of the incidence of cancer of the lung and larynx~~ based on data derived from ~~the~~ death certificates of cases of cancer of the lung and of the larynx in males from England and Wales for the ~~18 year~~ period 1921-1938. The study ~~is~~ was based on 38,418 certificates that were examined individually. This comprised 23,549 cases of cancer of the lung and 14,869 cases of cancer of the larynx. Their lengthy study should be examined for statistical particulars. These authors discuss at length the sources of error existing in a statistical work on death certificates, and the problems in studying occupational histories. These ~~workers~~ concluded after detailed analysis of their statistical material that the increase in recorded cases of lung cancer ~~cannot~~ could not be attributed to any increase of data obtained by autopsy.

Same of these workers found no special occupation among the 63 examined to which the ~~percent~~ increase in lung cancer incidence could be attributed.

Mason (1949) studied the occupational histories of 1,000 consecutive cases of lung cancer seen at the Northern Regional Chest Surgery Centre (England) during the years 1948-1949, and concluded that a great number of occupational groups was represented, and that no one could be singled out as being of etiological significance.

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Kösch (1950) reviewed 20,743 autopsies at the Düsseldorf Pathological Institute during the period 1920-1948 with regard to the incidence of cancer and of lung cancer in particular. This worker concluded that consideration of the occupational histories of these autopsied cases of lung cancer were of little value in determining a possible etiologic factor for human lung cancer.

ni Kösch

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Occupational histories have been tabulated in many studies of lung cancer. However, many such studies have not been considered in the previous pages, as the value of the occupational data is limited either because only a small number of cases are analyzed, or because control data are lacking as to the occupational distribution of the general population. Macklin (1948) has emphasized this latter point in the statement:

> "Once sees papers ... that in a given district lung cancer is oftenest found in the workers in the pottery factories; in other districts, lung cancer will be said to occur most exclusively in the coal miners, etc. Accompanying this should be a statement as to what percentage of the male workers in the first community were from the pottery plants; in the second, what percentage of the male workers in the district were coal miners. As long as we do not control our data, by asking the dame questions of those not suffering from the disease as are asked of patients with the disease, we cannot legitimately assume that the positive history of a trait has any significance."

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Hueper (1950) observed that, "the present inability of demonstrating a single extrinsic agent to be wholly responsible for ... [the increase in lung cancer] ... is not a valid reason against ~~this conception~~ [the operation of extrinsic factors] because it is well known that several agents with highly different physical and chemical properties may cause pulmonary malignancies of occupational origin."

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Macklin and Macklin (1950) critically discussed the methods employed in studying the role of occupational and environmental factors in lung cancer. They pointed out that many clinical investigators are not consistent in their questionaire forms. For example, lung cancer patients are asked about history of respiratory diseases, but uterine cancer cases are not questioned with regard to this. They observed that if one asked skin cancer patients about exposure to weather, a high degree of association will be obtained. But if one asked the same question of bladder cancer cases, a high percentage of association may also be found. They also pointed out that all occupations of patients must be examined as an early occupation may be more important than the most recent one. They observed that the statistical treatment of lung cancer by many workers has been faulty as the data is uncorrected for age and sex distribution, and further, that the mistake is often made of assuming that an unselected group of persons furnishes an adequate control merely because it is unselected. Macklin and Macklin emphasize that control groups must confirm with the experimental group in as many variables as possible except the one under direct study. These workers concluded that a wide variety of predisposing causes of lung cancer has been predicted, but no few systems has an adequately controlled study been made

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FINDINGS ON ENVIRONMENTAL & OCCUPATIONAL FACTORS IN LUNG CANCER:

The realization that in the male the incidence of bronchiogenic carcinoma is higher and is increasing faster than in the female, has focused attention on the possible role of occupational and environmental factors in the causation of this condition. Some evidence does suggest that such factors are operative in specific occupational circumstances. However, the present state of our knowledge makes it impossible to assign etiological significance to any particular factor that would account for the progressive and general increase in lung cancer incidence throughout the world. Many investigators have suggested the possible importance of air pollution by various substances — especially those associated with increasing industrialization or urbanization. However, in most reports comparing the incidence in rural areas with urban communities, the data presented show no difference in the incidence of the ~~dease~~ disease that can be accorded statistical significance. On the other hand the inadequacies of such data do not preclude the possible importance of air pollution .

The present reviewer agrees with many workers that more extensive and better controlled statistical information is necessary before a correlation can be considered as demonstrated between environmental and occupational factors and the incidence of lung cancer generally. A possible exception to this last statement may be raised in specific occupational instances where exposure to an agent in adequate concentration has been ascertained (chromates, radioactive ores, etc.).

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CHAPTER V

ALLEGED NEOPLASTIC RESPONSE OF ANIMALS TO TOBACCO AND ITS COMBUSTION PRODUCTS

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COMBUSTION TEMPERATURES IN THE SMOKING OF TOBACCO:

During the smoking process, tobacco is subjected to mild destructive distillation followed by combustion at temperatures in the range 370 - 700° C. Cooper and co-workers (1932), Kennaway (1925), and C ampbell (1939) among other workers have reported carcinogenic activity in animals in various organic materials burnt or destructively distilled in this temperature range. Copper and co-workers (1932) and Kennaway (1925) have reported slight carcinogenic activity in animals for tars obtained by the destructive distillation of coal and certain other organic materials at temperatures as low as 450° C. Tars obtained from coal heated at 560° C. were almost as carcinogenic as those produced at a temperature of 1250° C. Cooper and co-workers (1932) observed that in pipes smoked normally the temperature of combustion varied from about 370° to 590° C. according to the variety of tobacco used. With vigorous smoking, temperatures from 480° to 700° C. were observed. McNally (1932) observed a temperature of about 300° at the burning end of a cigarette dropping to 60° within 1.25 centimeters of the glowing zone. Lehmann (;) reported the temperature of the glowing zone in cigarettes to be about 400° falling to 70° C. at a distance of one centimeter from the mouth. In cigars, this worker reported thd corresponding values to be 300° and 35° C., respectively. Flory (1941) found that tobacco burning slowly in a pipe reached a temperature from 425° to 560° C., but during suction the temperature rose to 600° - 700° C., in isolated cases reaching 750° C. During suction temperatures in the glowing zone of cigarettes were recorded between 604° and 670° C. In contrast, the temperatures recorded for burning matches ranged from 850° to almost 1000° C.

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EARLY ~~ANIMAL~~ STUDIES ~~OF~~ ON TOBACCO AS A ~~POSSIBLE~~ NEOPLASTIC AGENT IN ANIMALS 147

Brosch (1900) painted the skin of guinea pigs or rabbits with tobacco juice and observed only proliferation of tissue.

Zborowski (1908) exppsed four rabbits to an atmosphere containing cigarette smoke (continuously ?). Two of the animals died after 57 and 66 days, respectively, and the remaining two were killed and autopsied at 129 and 180 days. Zborowski reported that on autopsy histologic changes were evident in the heart ganglia and in the aorta walls, but he did not state whether or not the animals were examined for atypical growths. Stöcker and Wacker (1910) painted the ears of rabbits with pyridine, a constituent of tobacco smoke, and reported that some epithelial growth was observed.

Wacker and Schmincke (1911, 1912) injected tobacco tar (from pipes) into the skin of rabbits' ears, and after about 21 days ~~he found~~ tissue proliferation was found which on histologic examination was misleadingly similiar to "laminellar skin cancer" and showed numerous branching of the proliferated epithelial cilia into the vicinity of the cartilage.

Hoffman, Schreus and Zurhelle (1923a) painted the skin of ~~animals~~ mice repeatedly with denicotinized, tobacco tar. After one week the hair fell out, and after two weeks dry yellow-brown flakes and crusts formed on the shiny depilated skin as a first sign of hyperkeratosis. This condition remissed, but soon as the hair started to grow back, it often fell out again. The painting with tobacco tar was continued for eighty days without any deep change in the

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skin except for inflammatory infiltrations under the derma and slight thickening of the epidermis. No atypical proliferation or malignant growth were observed. In further work, Hoffman, Schreus and Zurhelle (1923b) painted the skin of fowls with tobacco tar and produced only hyperkeratosis.

Bergerhoff (1923?) painted the skin (?) of mice for eighty days with a denicotinized, tobacco tar and observed neither malignant nor atypical epithelial growth.

Helwig (1928) injected rabbits with tobacco tar from pipes and observed only proliferation of tissue during a period of four months. He also painted inbred albino mice three times weekly with a nicotine-free ether extract of pipe tar in olive oil and with the destructive distillate of tobacco (400°- 500° fraction) and over a period of eight to ten months observed the formation of occasional benign ulcers. Helwig (1928) also called attention to work of Leitch of the Cancer Hospital Research Institute (apparently unpublished) in which the chloroform-soluble fraction of condensed tar from tobacco smoke was painted on animals with the appearance of ulceration, but of no epithelial proliferation.

Mertens (1930) exposed 125 male and female mice of various strains to an atmosphere of cigarette smoke for one to four hours daily. Apparently no control animals were employed. At the end of the experiment 28 animals were still alive. Five of these had been exposed to the action of the smoke for fifteen months, and were normal in weight and size. One animal died on the sixth day of the experiment (third day of smoking) and on autopsy pulmonary adenocarcinoma was demonstrated histologically. Mertens concluded that this

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neoplasm was present in the animal before institution of the experiment. A second animal succumbed on the 149th day of exposure the experiment after exposure to cigarette smoke for 110 hours on 111 days and on autopsy the findings were pulmonary adenocarcinoma with no metastasis to distant parts. Because only two neoplasms had been observed and because one probably pre-existed the experiment, Mertens held any consideration of a relationship between the action of the tobacco smoke and the causation of of the neoplasms was moot. Most of the animals exposed to the smoke showed various degrees of acute inflammation of the trachea, bronchi and lungs, and many succumbed to the smoke at early stages in the experiment. Changes were also observed in the spleen, skin, and intestines of some mice. During the course of the experiment few of the females became pregnant (one aborted) and the reason for this abnormality was not determined, however, some evidence of testicular changes was obtained. Mertens (1941) reported an extension of this series to more additional animals and to longer exposures to the tobacco smoke; this more recent paper is discussed in a later section of this chapter.

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Mertens (1941) reported tardily the continuation his study of the action of smoke on mice to more animals and to longer exposures ~~of~~ to tobacco smoke. ~~The earlier study (Mertens, 1931) has already been discussed in the section of this chapter entitled "Early Animal Studies of Tobacco as a Possible Neoplastic Agent".~~ A total of 157 mice of various strains, including 28 mice previously reported as surving periods of exposure to cigarette smoke up to fifteen months, were exposed to such smoke for usually two or three hours daily, but sometimes for five to seven hours. The total days of exposure to tobacco smoke in some animals was a maximum of 475 days. Of the 157 animals, 74 were subject to the smoke alone, 83 were also painted with tar (coal?), the tar treatment beginning two or three months before the action of smoke in some mice and simultaneously in others. The tar exerted no observable influence on the experimental findings. The development of cancerous growths in the respiratory system was observed in none of the animals, However, some metaplasia of the trachea and bronchi was observed. Mertens concluded that any relationship between smoking and lung cancer - whether positive or negative in sense - can only be evaluated when the experimental conditions can entirely duplicate the smoking process in man. He also observed that the small life span of the usual experimental animals presents an experimental difficulty.

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Roffo (1930a, 1930b, 1931a) reported that blowing smoke directly upon the mucous membrane of the rabbit's lip produced occasional superficial leukoplakia. Daily painting of the ears of rabbits with water in which tobacco smoke was condensed for a period of six to eight months resulted in the formation of a "papillary carcinoma" of the ear. Keratinization took place during the subsequent two months and the animal died one month later of pneumonia. There was no mention of metastases of the growth. Roffo (1931b) injected rabbits with pure nicotine or with crude nicotine extracted from tobacco, but was unable to produce either epithelial lesions or tumors during a period of eight to twelve months.

In 1931, Chikamatsu reported that by painting the ears of rabbits and the backs of mice with tobacco tars (unspecified as to mode of production), after 225 days a medullary cancer in a rabbit's stomach and a cancroid of a rabbit's ear were produced. The appearance of metastases was not mentioned. The tar was apparently inactive on mice as no positive results were recorded. The detailed number of animals employed and the experimental conditions were not reported. In contrast to the findings with tobacco tar, carcinomatous growth was observed on the ears of control rabbits painted with coal tar after sixty to ninety days (one-fourth of the time required before any effects of the tobacco tar were detected).

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Cooper and co-workers (1932) painted mice with tar from condensed whole smoke and from the destructive distillation of tobacco at 400-600° and at 700-800°C. These tars were extracted to free them of bases, acids, phenols and nicotine and thus to render them less toxic to the animals. They were applied as ten to fifty percent solutions in alcohol, benzene or glycerin. Fifty mice of unspecified strain were painted over a period of 23 months. One developed an epithelioma after sixteen months. This finding is to be compared with the findings of the same workers in apparently the same strain of mice that coal tars produced a high incidence of malignant growths. These workers concluded that tobacco tars are relatively unimportant in the causation of cancer. Spectrographic examination of the tobacco tars showed no bands characteristic of the benzpyrene type of carcinogenic agent. However, as the spectra were confused, they concluded that this observation was to be considered inconclusive.

Roffo (1931b, 1932) allowed tobacco smoke to impinge directly on the inner side of rabbits' ears. The animals were exposed to the influence of the smoke for two to three minutes daily. Roffo reported that after three years a carcinoma developed in one out of ten rabbits. Histologically it was shown to be a growing tumor with pronounced atypicity of its cells. Furthermore there was infiltration and perforation of the auricular cartilage with metastates to the cervical glands. Roffo (1932) introduced pills containing the combustion products of tobacco into the bladders of rats and reported the development of severe [illegible] lesions of

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a neoplastic type after eight to ten months. These lesions were more severe than those produced by pills containing tar, tricresol, ~~xxx~~ or aniline.

Moratti (1932) inserted cigars into the gall bladder of dogs and injected nicotine solutions into their breast for an unspecified period of time. By these procedures he obtained only chronic inflammation.

Bogen and Loomis (1932) painted the back of the neck of inbred mice and rabbits over a period of six to twelve months ~~xxx~~ with a glycerin solution of denicotined tar from the destructive distillation of cigarette tobacco at a temperature of 400-500° C. Loss of hair occurred in a few animals, but the hair soon reappeared. There was no thickening of the skin and no sign of the formation of cutaneous horns, warts or other proliferations during a period of more than one year. Control animals were treated with gashouse tar of known carcinogenic activity. The skin of these animals showed marked changes within a short time and within a few months small wart-like or papillary growths appeared, followed by more extensive and invasive growths that metastasized eventually. This latter demontrated that the inbred strain employed was highly susceptible to carcinogenic agents. In a further experiment, Bogen and Loomis painted the left ears of two rabbits with tobacco tar, and the right ears with gashouse tar. The ears painted with tobacco tar remained smooth, soft and pliable with no epithelial proliferation. The ears treated with gashouse tar [illegible] leading to [illegible]

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McNally (1938) made up the water-soluble products from the smoke of 100 cigarettes to a volume of 100 cubic centimeters and sprayed 0.1 cubic centimeters daily into the mouths of six half-grown rats. After 71 days, one rat died with two areas of inflammation on the tongue caused by encysted Trichinella spiralis. After 97 days another rat died, but autopsy did not reveal anything noteworthy. Six other rats had tobacco tar applied to the left ear and and six more had it applied to the shaved back. Two animals served as controls. Three rats with tarred backs died on the eighth day of nicotine poisoning, and the tar dosage was reduced in the remaining animals. After 110 days, three rats with tarred backs became ill and lost weight, and the tar treatment was discontinued. Hair grew in again as soon as tarring ceased. All of the experimental rats had coarser hair than the controls, but their growth was less rapid. As Poulson (1949) observed the intercurrent mortality and the relative brief experimental time even for the most long-lived animals makes McNally results indecisive.

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Lu (1934a, 1934b) painted tobacco tar daily on the inner side of both ears of rabbits. Of ten animals, two died within sixty days. The remaining eight animals showed no tumor formation at the end of 120 days. At this time painting of the left ears with coal tar two or three times weekly was begun while painting of the right ears was continued with tobacco tar. Four of the animals developed carcinomatous growths (confirmed histologically) on their left ear that had been painted with coal tar within 17 to 32 days after initiation of such painting. Three of these four animals showed evidence of carcinoma on their right ears that had been painted with tobacco tar after the 148th to the 168th day of such painting. None of the remaining four animals developed carcinoma from the coal tar application or the tobacco tar painting up to the 195th day of tobacco tar painting. On this day one rabbit of the four developed a carcinoma on the ear painted with coal tar. Lu surmised that this tumor might be associated with the intravenous injection of cholesterol in olive oil daily from the 185th day for eight days. To check this relationship he devised further experiments.

Lu pretreated six rabbits with daily intravenous injections of cholesterol (1 cubic centimeter of a 3 percent solution in olive oil). Two animals died of lung embolism. The remaining four were painted daily on their left ear with coal tar and on their right ear with tobacco tar. Tumors were observed on the left ear ear on the [illegible] to [illegible]th day of painting, and were identified as carcinoma on the [illegible]7th to [illegible]th day. No tumors were observed on the right ears that were [illegible] tobacco tar [illegible] included

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pre-treatment with massive doses of cholesterol speeded the appearance of coal tar tumors, but did not elicit any carcinogenic action for tobacco tar. Daily painting of the ears of twox rabbits with an aqueous solution of tobacco smoke produced no effect.

(1935) Schürch and Winterstein (1935) observed no tumor formation by painting mice during a period of 258 to 635 days with denicotinized tar from cigar smoke alone or in combination with mechanical or thermal injury. Further, there was no tumor growth by painting mice over a period of 60 to 480 days with distillates of the cigar tar mentioned above. Also they found no ill effects by painting the ears of rabbits for a period of 223 days and painting the mouths of rabbits over a period of 540 days with the cigar tar. They also painted one ear of rabbits maintained on a cholesterol-rich diet with coal tar until papillomas appeared. These painted ears were amputated, and the other ear was painted with tar from cigar smoke. In this latter series among seven survivors out of ten rabbits, one animal developed a carcinoma after 344 days and six developed papillomas after 161 to 700 days. Later Schürch and Winterstein (1937) applied coal tar to one ear of rabbits until warts appeared at which time the ear was amputated and applied tar from cigar smoke to the other ear for a period of 48 months. The animals were maintained on a cholesterol-rich diet. There appeared a squamous carcinoma on the ear of one rabbit as well as a papilloma on the nictitating membrane, multiple hemangiomata of the intestine and a spindle cell sarcoma of the rectum. Wart formation occurred in two rabbits. These workers (Schürch

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detect
found on spectrographic analysis of tobacco tar any known aromatic, fused ring hydrocarbons (that is, carcinogens of the dibenzanthracene or benzpyrene type).

Campbell (1934, 1936) used strains of mice predisposed to a high incidence of spontaneous lung tumors. He exposed them to cigaret smoke under conditions resembling those of a more than moderate human cigaret smoker in the amount of smoke inhaled. There was no effect of any importance upon death rate, body weight, fertility, or rate of growth. Seventeen of 74 experimental mice and 11 of 76 control animals developed primary lung tumors. The higher incidence in the animals exposed to tobacco smoke was not considered significant because a few animals in the experimental group survived for a longer period than those in the control group. Campbell (1934, 1936, 1939) painted mice for about sixteen months with tar condensed from cigaret smoke and reported the appearance of occasional hyperplasia and possible skin neoplasia.

According to Kinoshita (1937), Taki painted mice with a denicotinized ether extract of tobacco tar from Japanese pipes (clay?) for periods up to 130 days, and observed two squamous epitheliomas and three papillomas. Other experimental conditions and findings were not recorded.

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